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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,808	08/04/2003	Alexander V. Sokoloff	Mirus.014.04.1	8504

25032 7590 04/20/2005

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EXAMINER	
DESAI, ANAND U	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,808	SOKOLOFF ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12-15,18 and 20-30* is/are rejected.

7)☒ Claim(s) *2-11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

MC

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, drawn to a composition comprising a T7 ligand attached to a compound, wherein the T7 ligand is attached to the compound through a covalent bond, in the reply filed on February 1, 2005 is acknowledged. Applicants further elect with traverse a "complex" compound and a T7 p17 derived peptide as a species of the composition to be searched. The traversal is on the ground(s) that for any ligand to direct a compound to a specific site, the ligand must be linked to the compound through only two methods available, either covalent or non-covalent interaction. Both methods of linkage being well known in the art. It is Applicants' opinion that the elected species describing the attached compound are obvious variants of one another. It is Applicants' opinion that the elected T7 ligand identified as SEQ ID NO: 1, T7 phage, T7 p17 protein, and T7 p17 derived peptide are obvious variants of one another. This is not found persuasive because the composition being claimed in the two groups are composed of different structures, a compound bound to a T7 ligand through a covalent bond and a compound bound to a T7 ligand through a non-covalent interaction. The covalent composition would have a different mode of operation than the non-covalent composition. The requirement is still deemed proper and is therefore made FINAL.

2. Claim 19 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 1, 2005. This application contains claim 19 drawn to an invention nonelected with traverse. A complete

reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. The priority date is August 5, 2002.

Information Disclosure Statement

4. The information disclosure statements (IDSs) submitted on May 21, 2004 and August 7, 2004 appear to be duplicates. The August 7, 2004 IDS is being considered by the examiner, because the corresponding submission letter was signed by the attorney.

Specification

5. The disclosure is objected to because of the following informalities:

6. On page 43, lines 14-15, the sentence is missing the "to" prior to the word, "complexes."

7. The use of the trademark pharmaceuticals has been noted in this application. Particularly, on page 14 beginning on line 23. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Objections

8. Claims 2-11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

9. The term "T7 ligand" is being defined as a ligand selected from the group consisting of: a T7 phage, a T7 p17 protein, a fragment of the T7 p17 protein, a T7 p17 rod-domain, a peptide fragment of the p17 rod-domain, or a synthetic analog of this peptide as described in paragraph 0006 of the U.S. Publication of the current application.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 18, and 20-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. In claims 1, 18, 20, 29, and 30, what is the "compound?" In claim 1, how is the ligand attached to the compound?

13. In claim 21, the word, polyethylene glycol, should be spelled out as at its first occurrence prior to the abbreviation, PEG.

14. In claims 29, and 30, how are the "compound" and the "T7 ligand" associated?

15. Claims 22-28 are rejected because they depend from a rejected base claim, and they do not cure the indefiniteness of the "compound" of independent claim 1.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a **composition** comprising a T7 ligand attached to a compound, does not reasonably provide enablement for a **pharmaceutical** preparation comprising any compound associated with a T7 ligand, and a composition which targets hepatocytes *in vivo* comprising a T7 ligand associated with any compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement:

1.) The nature of the invention: The invention is drawn to a composition comprising a T7 ligand attached to any compound through a covalent bond, a pharmaceutical preparation comprising any compound associated with a T7 ligand, and a composition for targeting hepatocytes *in vivo* comprising a T7 ligand associated with any compound.

2.) The breadth of the claims: The claims are broad in that any T7 ligand can be associated to any compound to function as a pharmaceutical preparation or for targeting to hepatocytes *in vivo*.

4.) & 5.) The amount of direction or guidance presented/The presence or absence of working examples: The specification provides examples which describe trafficking of bioactive molecules to the liver and hepatocytes of mice, and monkey using various compositions

comprising either a T7 phage, a T7 phage p17 protein, or a T7 phage p17 protein rod domain associated with exogenous cargo, such as avidin, plasmid DNA encoding human factor IX expression cassette, fluorescent-streptavidin/gold particles, and a pH-labile anionic polymer. The specification describes experimental steps that may be used to identify the T7 ligand receptor responsible for hepatocyte targeting. The specification describes a method of using a T7 phage display library to determine the hepatocyte targeting consensus sequence. The specification describes experiments to investigate the coiled coil structural feature of p17 for hepatocyte targeting.

3.) & 6.) & 7.) The predictability or unpredictability of the art/The quantity of experimentation necessary/The state of the prior art: There is unpredictability in the ability of designing pharmaceutical that can selectively target tissues, including hepatocytes *in vivo*. There is a large quantity of experimentation necessary when designing pharmaceutical compositions for delivery; It is advisable to test drug-delivery preparations with regard to possible immunogenicity in an early stage of development, since major problems may occur especially with chronic dosing; Cell-specific distribution of the drug-targeting preparations as well as the rate of drug release from the carrier should be studied in vivo both in normal and the pathological situation. It is of prime importance to check if the chosen drug-targeting concept is also valid in the disease state. Generally the development of a drug-targeting preparation requires an integrated multidisciplinary approach: cell biology should go hand-in-hand with medicinal chemistry, pharmaceutical technology, and clinical medicine. Potential problems of large-scale preparations, and clinical phase I and phase II testing should be anticipated (see Meijer, D. et al. Antiviral Research 18:215-258 (1992), particularly page 219, General guidelines

in drug delivery research). Further, the state of the art has shown that liposome-mediated gene delivery to the liver is more difficult than to other organs, such as to lungs. Liposome-mediated gene delivery is still in its infancy due to difficulties in solving general issues, such as the circulatory stability of liposome-DNA complexes, and lysosomal or endosomal degradation of plasmid DNA (see Wu, J. et al. Frontiers in Bioscience 7: 717-725 (2002), particularly Abstract).

8.) In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a doctoral scientist with several years of experience in the art. As the cited art would point to, even with a level of skill in the art, which is of a doctoral scientist, predictability of the results is not invariable. In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

18. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to a fragment of the rod domain. To satisfy the written description requirement, the specification must describe the invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. The specification does not sufficiently describe the structure, that is amino acids in the various

polypeptides that can be altered without affecting the function of a specific polypeptide. For one to be in possession of the claimed invention, the inventor would have to know the functional consequences of structural alterations. Thus due to the limited predictability in the art, a skilled artisan would not find adequate support for a fragment of the rod domain as disclosed in claim 26 in the specification.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 1, 12-15, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Studier, F. (Virology 39: 562-574 (1969)).

Studier, F. discloses a composition comprising a T7 ligand attached to a compound. The plating of T7 bacteriophage on E. coli. could be reasonably interpreted to describe a composition comprising a T7 ligand attached to a compound, where the T7 ligand consists of a T7 phage, the T7 phage comprises SEQ ID NO: 1, and the bacteria is a compound (see Materials and Methods section, page 565, Plating of T7, current application, claims 1, 12-15, and 22).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON WEBER
SUPERVISORY PATENT EXAMINER

April 15, 2005